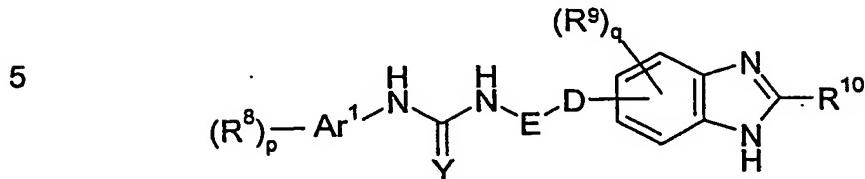


Claims

1. Benzimidazolyl derivatives of formula I



wherein

10

Ar^1 is selected from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

15

E is $(\text{CR}^5\text{R}^6)_n$, wherein n is 1 or 2,

D is $(\text{CR}^5\text{R}^6)_k$, wherein k is 0 or 1,

20

R^5 , R^6 are in each case independently selected from H and A;

25

R^8 , R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, $\text{C}(\text{Hal})_3$, NO_2 , $(\text{CH}_2)_n\text{CN}$, OHet, $\text{N}(\text{R}^{11})\text{Het}$, $\text{NR}^{11}\text{COR}^{13}$, $\text{NR}^{11}\text{COOR}^{13}$, $\text{CONR}^{11}\text{R}^{12}$, COOR^{13} , $(\text{CR}^5\text{R}^6)_k\text{Het}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{Het}$, $\text{N}(\text{R}^{11})(\text{CR}^5\text{R}^6)_k\text{Het}$, $(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{NR}^{11}\text{R}^{12}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{R}^{13}$, $\text{O}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $\text{NR}^{11}(\text{CR}^5\text{R}^6)_k\text{OR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{OR}^{11}$, $(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$,

30

(CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹²,
 (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹,
 CH=N-OA, CH₂CH=N-OA, (CH₂)_nNHOA, (CH₂)_nCH=N-R¹¹,
 (CH₂)_nOC(O)NR¹¹R¹², (CH₂)_nNR¹¹COOR¹³,
 5 (CH₂)_nN(R¹¹)CH₂CH₂OR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OCF₃,
 (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹², (CH₂)_nN(R¹¹)C(R¹³)HCOR¹¹,
 (CH₂)_nN(R¹¹)CH₂CH₂N(R¹²)CH₂COOR¹¹,
 (CH₂)_nN(R¹¹)CH₂CH₂NR¹¹R¹², CH=CHCOOR¹³,
 CH=CHCH₂NR¹¹R¹², CH=CHCH₂NR¹¹R¹², CH=CHCH₂OR¹³,
 10 (CH₂)_nN(COOR¹³)COOR¹⁴, (CH₂)_nN(CONH₂)COOR¹³,
 (CH₂)_nN(CONH₂)CONH₂, (CH₂)_nN(CH₂COOR¹³)COOR¹⁴,
 (CH₂)_nN(CH₂CONH₂)COOR¹³, (CH₂)_nN(CH₂CONH₂)CONH₂,
 (CH₂)_nCHR¹³COR¹⁴, (CH₂)_nCHR¹³COOR¹⁴, (CH₂)_nCHR¹³CH₂OR¹⁴,
 (CH₂)_nOCN and (CH₂)_nNCO, wherein

15 R¹¹, R¹² are independently selected from a group consisting of H,
 A, (CH₂)_mAr³ and (CH₂)_mHet, or in NR¹¹R¹²,

20 R¹¹ and R¹² form, together with the N-atom they are bound to, a 5-, 6-
 or 7- membered heterocyclo which optionally contains 1 or 2
 additional hetero atoms, selected from N, O and S,

R¹³, R¹⁴ are independently selected from a group consisting of H,
 Hal, A, (CH₂)_mAr⁴ and (CH₂)_mHet,

25 A is selected from the group consisting of alkyl, alkenyl, cycloalkyl,
 alkylene cycloalkyl, alkoxy, alkoxyalkyl and saturated heterocycl,
 preferably from the group consisting of alkyl, alkenyl, cycloalkyl,
 alkylene cycloalkyl, alkoxy and alkoxyalkyl,

30 Ar³, Ar⁴ are independently from one another aromatic hydrocarbon
 residues comprising 5 to 12 and preferably 5 to 10 carbon atoms

which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

5

Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one ore more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂NR¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

10

R¹⁵, R¹⁶ are independently selected from a group consisting of H, A, and (CH₂)_mAr⁶, wherein

15

Ar⁶ is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,

20

k, n and m are independently of one another 0, 1, 2, 3, 4, or 5,

Y is selected from O, S, NR²¹, C(R²²)-NO₂, C(R²²)-CN and C(CN)₂, wherein

25

R²¹ is independently selected from the meanings given for R¹³, R¹⁴ and

R²² is independently selected from the meanings given for R¹¹, R¹²,

30

p is independently in each case 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

and

5

Hal is independently selected from a group consisting of F, Cl, Br and I;

10

the tautomeric forms therof; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

2. Benzimidazolyl derivatives according to claim 1,

wherein

15

Ar¹ is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

20

R⁸, R⁹ and R¹⁰ are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, OHet, N(R¹¹)Het, NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³, (CR⁵R⁶)_kHet, O(CR⁵R⁶)_kHet, N(R¹¹)(CR⁵R⁶)_kHet, (CR⁵R⁶)_kNR¹¹R¹², (CR⁵R⁶)_kOR¹³, O(CR⁵R⁶)_kNR¹¹R¹², NR¹¹(CR⁵R⁶)_kNR¹¹R¹², O(CR⁵R⁶)_kR¹³, NR¹¹(CR⁵R⁶)_kR¹³, O(CR⁵R⁶)_kOR¹³, NR¹¹(CR⁵R⁶)_kOR¹³, and/or are independently selected from a group consisting of NR¹¹COR¹³, NR¹¹COOR¹³, CONR¹¹R¹², COOR¹³, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nNR¹¹(CH₂)_kNR¹¹R¹², (CH₂)_nO(CH₂)_kOR¹¹, (CH₂)_nNR¹¹(CH₂)_kOR¹², (CH₂)_nCOR¹³,

25

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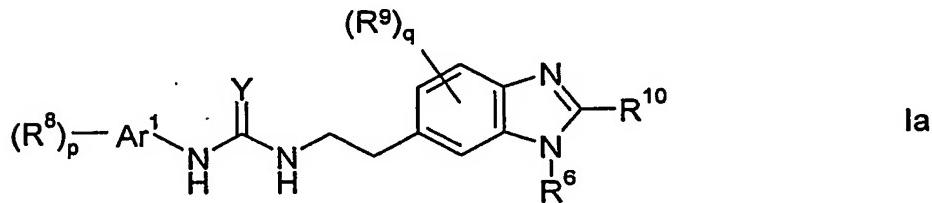
(CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³,
 (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹²,
 (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹,
 (CH₂)_nNHOA, (CH₂)_nNR¹¹COOR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OR¹³,
 5 (CH₂)_nN(R¹¹)CH₂CH₂OCF₃, (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹²,
 (CH₂)_nN(R¹¹)C(R¹³)HCOR¹¹, (CH₂)_nN(COOR¹³)COOR¹⁴,
 (CH₂)_nN(CONH₂)COOR¹³, (CH₂)_nN(CONH₂)CONH₂,
 (CH₂)_nN(CH₂COOR¹³)COOR¹⁴, (CH₂)_nN(CH₂CONH₂)COOR¹³,
 (CH₂)_nN(CH₂CONH₂)CONH₂, (CH₂)_nCHR¹³COR¹⁴,
 10 (CH₂)_nCHR¹³COOR¹⁴ and (CH₂)_nCHR¹³CH₂OR¹⁴,

p is 1, 2, 3 or 4, preferably 1, 2 or 3,

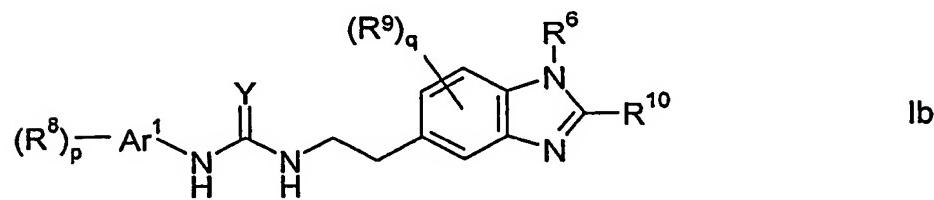
the tautomeric forms therof; and the pharmaceutically acceptable
 15 derivatives, solvates, salts and stereoisomers thereof

3. Benzimidazolyl derivative according to claim 1 or 2, selected from the compounds of formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, II, Ij, Ik, IL, Im, In, Io, Ip, Iq and Ir,

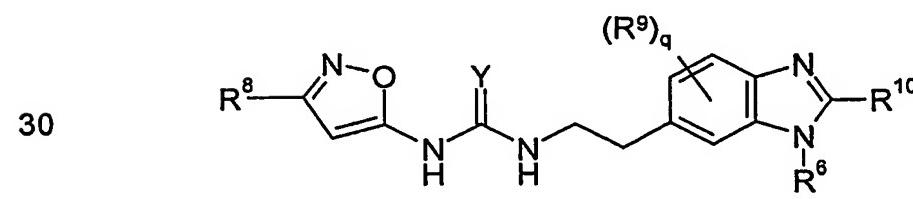
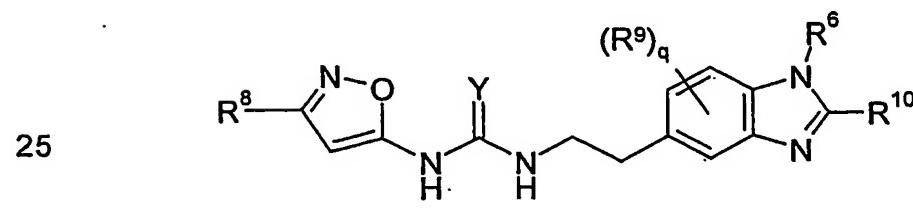
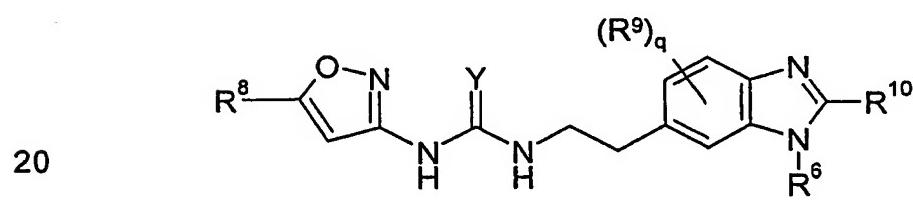
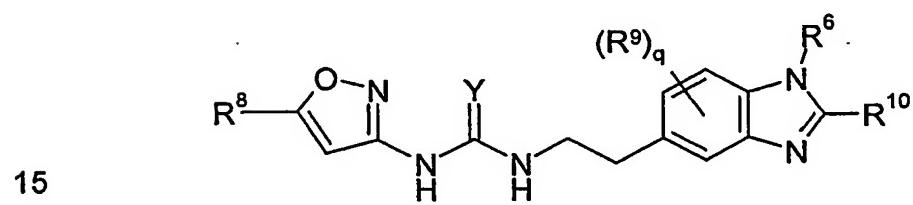
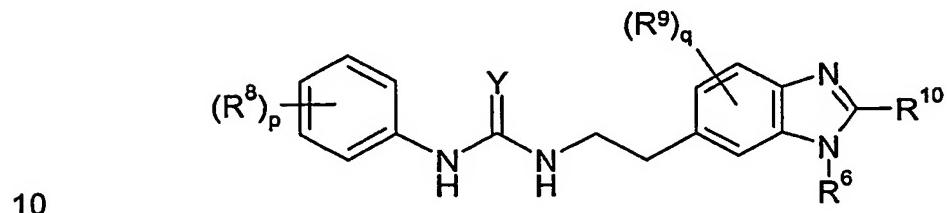
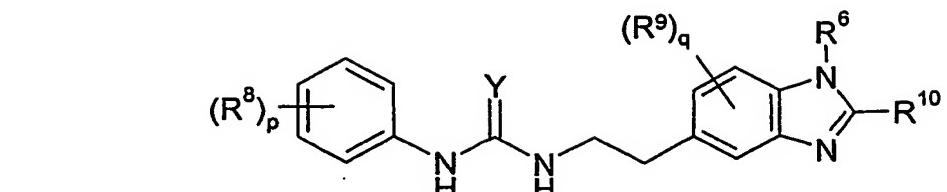
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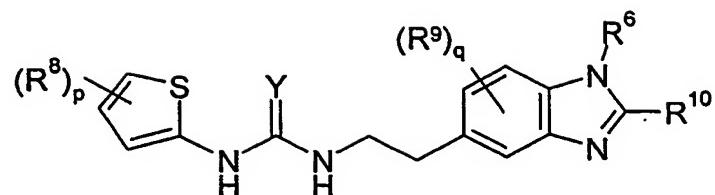


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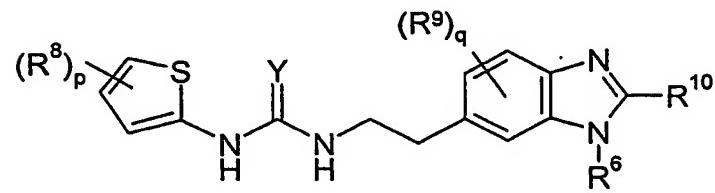
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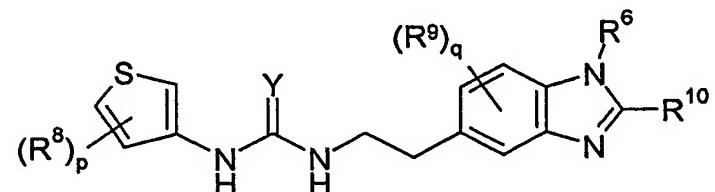
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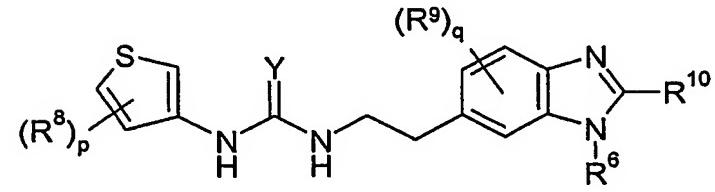
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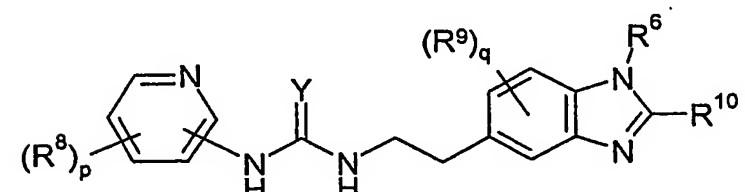
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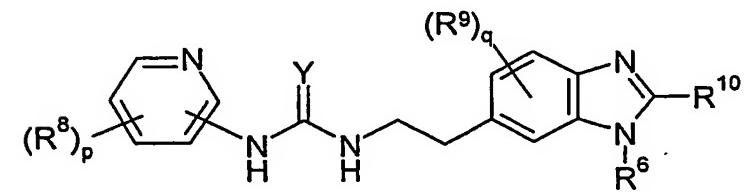
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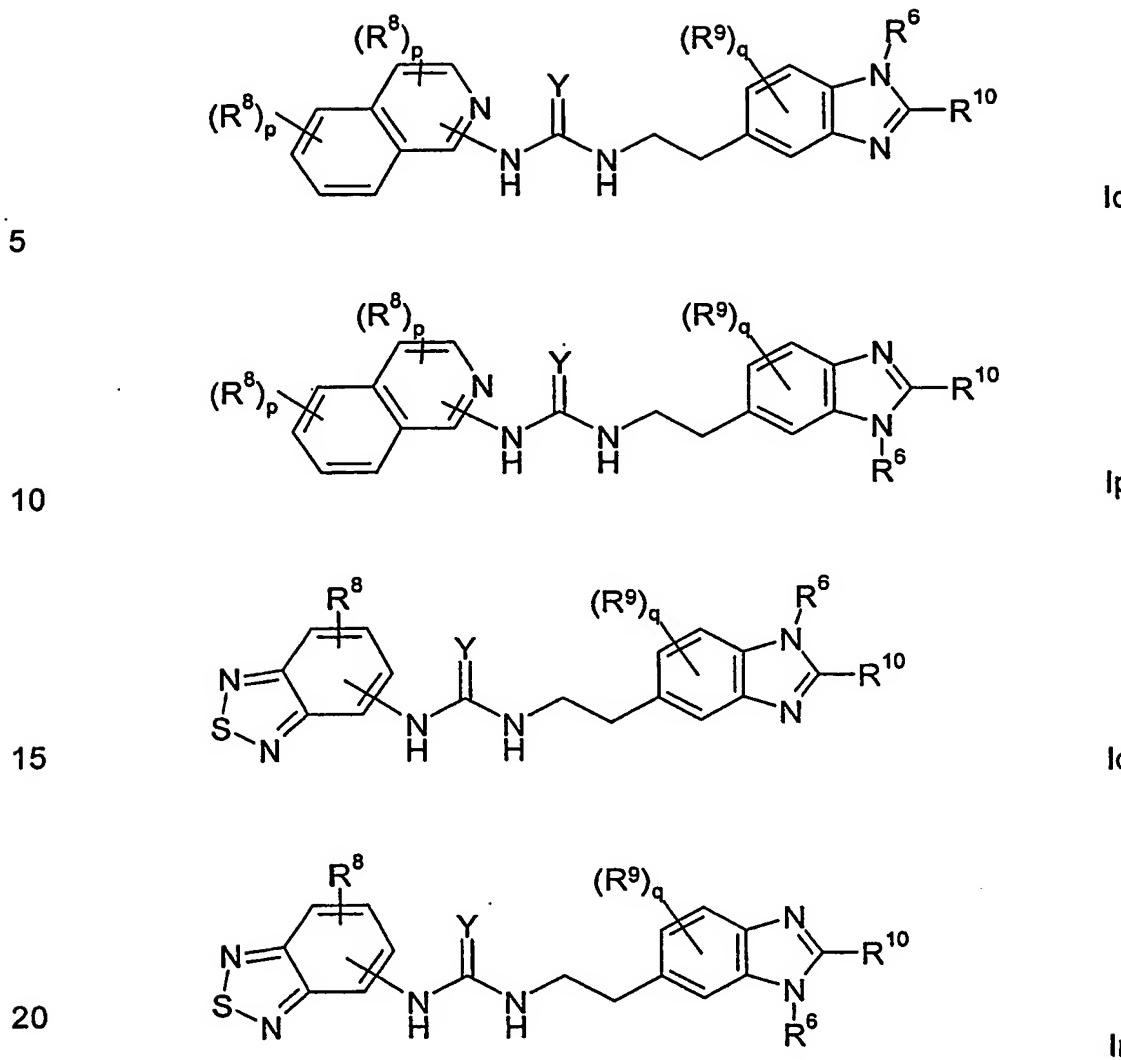


im

30



in



wherein R⁸, R⁹, R¹⁰, Y, p and q are as defined in claim 1 or 2, R¹⁰ is H or as defined in claim 1 or 2; the tautomeric forms therof; and the pharmaceutically acceptable derivatives, salts and solvates thereof.

25

4. Benzimidazolyl derivative according to claim one of the claims 1 to 3, selected from
 30 6-{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazole-2-carboxylic acid methylester,
 6-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazole-2-carboxylic acid methylester,

- 5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazole-2-carboxylic acid methylamide,
(5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester,
5 N-(5-{2-[3-(Methoxy-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide,
5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazole-2-carboxylic acid methylamide,
(5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-carbamic acid methyl ester,
10 N-(5-{2-[3-(Chloro-trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide;
1-[2-(2-Amino-1H-benzoimidazol-5-yl)-ethyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea;
15 N-(6-{2-[3-(4-Chloro-2-methoxy-5-methyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide;
N-[6-(2-{3-[2-(Pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
N-(6-{2-[3-(3-Chloro-4-methyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-
20 2-yl)-acetamide;
N-(6-{2-[3-(5-Chloro-2-methoxy-4-methyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide;
N-(6-{2-[3-(3-Trifluoromethyl-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide;
25 N-(6-{2-[3-(3,4-Dichloro-phenyl)-ureido]-ethyl}-1H-benzoimidazol-2-yl)-acetamide;
N-[6-(2-{3-[5-Methyl-2-(2-methylamino-ethoxy)-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
N-[6-(2-{3-[2-(2-Methylamino-ethoxy)-5-trifluoromethyl-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
30 N-[6-(2-{3-[2-(2-Amino-ethoxy)-4-chloro-5-methyl-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;

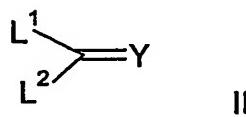
- N-[6-(2-{3-[2-(2-Amino-ethoxy)-4-chloro-5-trifluoromethyl-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
N-[6-(2-{3-[4-Chloro-5-methyl-2-(2-methylamino-ethoxy)-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
5 N-[6-(2-{3-[4-Chloro-2-(2-methylamino-ethoxy)-5-trifluoromethyl-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
N-[6-(2-{3-[2-(2-Amino-ethoxy)-5-trifluoromethyl-phenyl]-ureido}-ethyl)-1H-benzoimidazol-2-yl]-acetamide;
the tautomeric forms thereof; and the pharmaceutically acceptable
10 derivatives, salts and solvates thereof.
5. Benzimidazolyl derivative according to one of the claims 1 to 4 as a medicament.
- 15 6. Benzimidazolyl derivative according to one of the claims 1 to 4 as a kinase inhibitor.
7. Benzimidazolyl derivative according to claim 6, characterized in that the kinases are selected from raf-kinases, Tie-kinases, PDGFR-kinases
20 and VEGFR-kinases.
8. Pharmaceutical composition characterised in that it contains one or more compounds according to one of the claims 1 to 4.
- 25 9. Pharmaceutical composition according to claim 8, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 4.
- 30 10. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the

claims 1 to 4 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 4, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.

11. Use of a compound according to one of the claims 1 to 4 as a pharmaceutical.
12. Use of a compound according to one of the claims 1 to 4 in the treatment and/or prophylaxis of disorders.
13. Use of a compound according to one of the claims 1 to 4 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
14. Use according to claim 12 or 13, characterised in that the disorders are caused, mediated and/or propagated by one or more kinases, selected from raf-kinases, Tie-kinases, PDGFR-kinases and VEGFR-kinases.
15. Use according to claim 12, 13 or 14, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
16. Use according to claim 12, 13, 14 or 15, characterised in that the disorder is cancer.
17. Use according to claim 12, 13, 14 or 15, characterised in that the disorder is noncancerous.

18. Use according to claim 12, 13, 14, 15 or 17, characterised in that the disorders are selected from the group consisting of psoriasis, arthritis, inflammation, endometriosis, scarring, Helicobacter pylori infection, Influenza A, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
5
19. Use according to one of the claims 12 to 16, characterised in that the disorders are selected from the group consisting of melanoma, brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, ovarian cancer, ovary cancer, uterine cancer, prostate cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
10
15
20. Use according to one of the claims 12 to 17, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation, solid tumors, rheumatic arthritis, diabetic retinopathy, and neurodegenerative diseases.
20
25
21. Use according to one of the claims 12 to 15, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.
30
22. Use of a compound according to one of the claims 1 to 4 as a kinase inhibitor.

23. Use according to claim 22, characterised in that the kinase is one or more kinases selected from the group consisting of raf-kinases, Tie-kinases, PDGFR-kinases, VEGFR-kinases and p38-kinases.
- 5
24. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 4 is administered to a patient in need of such a treatment.
- 10
25. Method according to claim 24, characterised in that the one or more compounds according to one of the claims 1 to 4 are administered as a pharmaceutical composition according to claim 8 or 9.
- 15
26. Method for the treatment and/or prophylaxis of disorders according to claim 25, characterised in that the disorders are as defined in one of the claims 14 to 21.
27. Method for the treatment according to claim 26, characterised in that the disorder is cancerous cell growth mediated by raf-kinase, Tie kinases, PDGFR kinases and/or VEGFR kinases.
- 20
28. Method for producing compounds of formula I, characterised in that
- a) a compound of formula II,
- 25



30 wherein
L¹ and L² either independently from one another represent a leaving group, or together represent a leaving group, and Y is as

defined above/below,

is reacted with

- 5 b) a compound of formula III

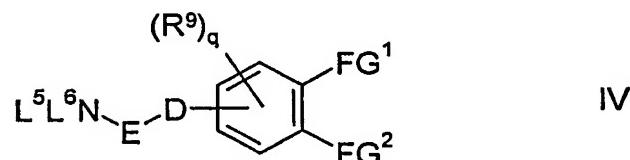


10 wherein

L^3 and L^4 are independently from one another H or a metal ion,
and wherein R^8 and p are as defined in claim 1,

and

- 15 c) a compound of formula IV,



wherein

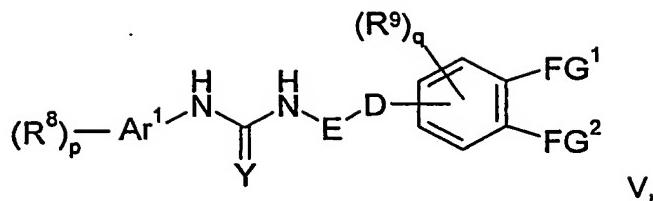
L^5 and L^6 are independently from one another H or a metal ion,

25 FG^1 is NHR^6 ,

FG^2 is NH_2 oder NO_2 ,

and E, D, R^9 , and q are as defined in claim 1, to obtain a
compound of formula V

30



- 10 d) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 , to transfer the NO_2 group into a NH_2 group, and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2 is NH_2 ,

with $\text{Hal}_3\text{C-C(=NH)OA}$ to obtain a compound of formula I, wherein R^{10} is CHal_3 ; or

with HalCN to obtain a compound of formula I, wherein R^{10} is NH_2 ;

15 e) and optionally transferring the compound obtained from step d) into a compound of formula I, wherein R^{10} is other than CHal_3 or NH_2 ,

f) and optionally isolating and/or treating the compound of formula I as obtained by said reaction, with an acid, to obtain the salt thereof.

20

29. Method for producing compounds of formula I, characterised in that

- a) a compound of formula IIIb

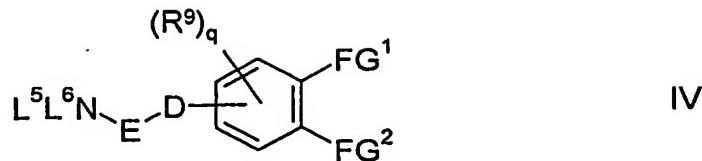
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wherein R⁸, Ar¹, p and Y are as defined in claim 1, is reacted with

30

- b) a compound of formula IV,



5

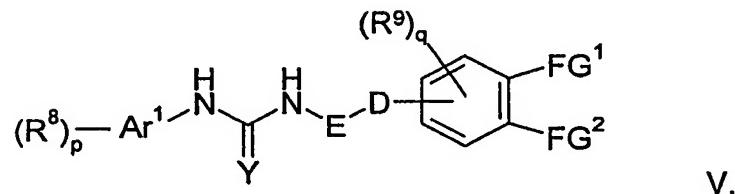
wherein

 L^5 and L^6 are independently from one another H or a metal ion, FG^1 is NHR^6 , FG^2 is NH_2 oder NO_2 ,

10

and E, D, R^9 , and q are as defined in claim 1, to obtain a compound of formula V

15



20

- c) subjecting the compound of formula V to a reduction step, if FG^2 is NO_2 , to transfer the NO_2 group into a NH_2 group, and reacting the compound of formula V, wherein FG^1 is NHR^6 and FG^2 is NH_2 ,

with $Hal_3C-C(=NH)OA$ to obtain a compound of formula I, wherein R^{10} is $CHal_3$; or

with $HalCN$ to obtain a compound of formula I, wherein R^{10} is NH_2 ;

25

- d) and optionally transferring the compound obtained from step c) into a compound of formula I, wherein R^{10} is other than $CHal_3$ or NH_2 ,

- e) and optionally isolating and/or treating the compound of formula I as obtained by said reaction, with an acid, to obtain the salt thereof.

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30. Compound of formula IIIb,

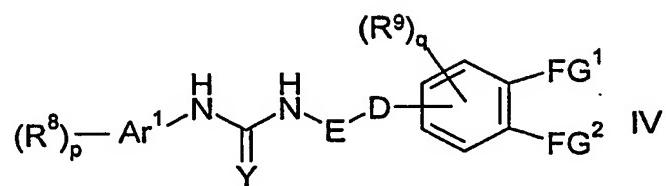


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wherein R^8 , p , Ar^1 and Y are as defined in claim 1.

31. Compound of formula IV,

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wherein

FG^1 is NHR^6 ,

FG^2 is NH_2 oder NO_2 ,

and E , D , R^9 , and q are as defined in claim 1.

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